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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/316,199	05/21/1999	Michael J McCluskie	C1040/7006HC	7506

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EXAMINER

POPA, ILEANA

ART UNIT	PAPER NUMBER
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1633

MAIL DATE	DELIVERY MODE
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11/09/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/316,199	MCCLUSKIE ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 July 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4-9,12,13,15-20,22,25-28,129,135-142 and 144-146 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-9,12,13,15-20,22,25-28,129,135-142 and 144-146 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10/15/2009; 02/20/2009</u> . | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1633

DETAILED ACTION

1. Claims 2, 3, 10, 11, 14, 21, 23, 24, 29-128, 130-134 and 143 have been cancelled.

Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 are pending and under examination.

Response to Arguments

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Art Unit: 1633

3. Claims 1, 5-9, 12, 15-18, 22, 129, 135-137, 139-142 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 5, 9-11, 13 and 14 of copending Application No. 10/300,247. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to a method of inducing a mucosal immune response by administering to a subject an oligonucleotide 8 to 100 nucleotides long and a viral antigen not encoded by a nucleic acid; the oligonucleotide has the formula 5' $X_1X_2CGX_3X_4$ 3', wherein C is unmethylated, X_1 , X_2 , X_3 , and X_4 are nucleotides, and both the oligonucleotide and the antigen are administered intranasally or ocularly (claims 1, 22, 129, 135-137, and 139-142). The antigen is delivered in colloidal dispersion systems (claims 5-7), the method further comprises administering a non-oligonucleotide adjuvant, such as MPL (claims 8 and 9), the subject is at risk of developing an infectious disease (claim 12), the oligonucleotide contains phosphorothioate modifications at the 5' end or the 3' end (claims 15-17), X_1X_2 could be GpT and X_3X_4 could be TpT (claim 18). The specification defines that the viral antigen could be a hepatitis B viral antigen and therefore, the vaccine could be used to elicit an immune response in a subject infected with hepatitis B therefore, i.e., the vaccine can be used to treat a subject infected with hepatitis B (p. 27, lines 14-23, p. 29, line 14, p. 40, lines 13 and 14).

The application claims recite a method of treating a subject infected with hepatitis via inducing an immune response against hepatitis virus by administering to the subject an oligonucleotide 8 to 100 nucleotides long, an antigen, and a non-nucleic acid adjuvant (claims 1, 4, and 12), wherein the non-nucleic acid adjuvant could be MPL (claim 5); the oligonucleotide has the formula 5' $X_1X_2CGX_3X_4$ 3' wherein C is unmethylated, X_1 , X_2 , X_3 , and X_4 are nucleotides, the oligonucleotide contains phosphorothioate modifications at the 5' end or the 3' end (claims 9-11 and 13), X_1X_2 could be GpT and X_3X_4 could be TpT (claim 14). The specification defines that the antigen could be a polypeptide (i.e., not encoded by a nucleic acid vector), the non-nucleic acid adjuvant could be a liposome (i.e., micellar, lipid-based system), and that the delivery could be intranasal or ocular (p. 3, lines 11 and 12, p. 16, lines 5-13, p. 27, lines 16 and 17).

Since the application claims embrace all the limitations of the instant claims, the application claims and the instant claims are obvious variants.

Applicant argues that the rebuttal of the provisional double patenting rejection is deferred until the cited co-pending application is allowed.

Applicant's argument is acknowledged; however, the rejections will be maintained until a Terminal Disclaimer is filed or claims are amended to obviate the rejection.

Art Unit: 1633

4. Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22 of the U.S. Patent No. 7,488,490 (filed as Application No. 10/023,909), in view of Craig. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The claims are obvious variants because both claim sets encompass a method of inducing mucosal immune response via administering to a subject a composition comprising an antigen, an oligonucleotide having the formula 5' X₁X₂CGX₃X₄ 3', wherein C is unmethylated and X₁, X₂, X₃, and X₄ are nucleotides, and a non-oligonucleotide adjuvant such as MPL. Although the patent claims recite inducing an immune response and not inducing a mucosal immune response as recited in the instant claims, the application specification discloses that the immune response encompasses a mucosal immune response (see p. 45 of the specification as filed). The patent claims do not recite further using B-7, as recited in the instant claim 25. Craig teaches using B-7 to upregulate the immune response to vaccines (column 6, lines 35-49). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the patent claims by further using B-7 costimulatory molecule, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to enhance the immune response elicited against the vaccine of interest. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that B-7 can be successfully used to potentate the immune responses to antigens.

Thus, the instant claims and the patent claims are obvious variants.

Applicant traversed the instant rejection on the grounds that, in order to find obviousness type double patenting, the rejected application claim must be obvious in view of the patent claim, in the absence of the teachings in other references and typically in the absence of teachings from the underlying patent specification.

In view of the foregoing, the basis for the double patenting rejection is flawed. First, the Examiner's reliance on Craig is clearly improper. The rejected claims must be found to be obvious over the patent claims independent of Craig. Second, the Examiner's reliance on the teachings of the underlying patent specification is also improper at least because the cited passage does not teach what it is purported to teach. The Examiner has stated that the passage on page 45 of the co-pending application 10/023,909 as filed "discloses that the immune response encompasses a mucosal immune response." The passage does not provide such a teaching. Instead the passage refers to administration routes for an adjuvant combination that include mucosal as well as non-mucosal routes. The passage does not define terms in the cited patent claims. The Examiner's reliance on this passage is improper.

Notwithstanding this, the rejected application claims are not obvious variants of the cited patent claims at least because the differences between the two claim sets would not be obvious to one of ordinary skill in the art. For example, the rejected application claims all recite induction of a mucosal immune response in subjects in need of a mucosal immune response. These limitations are not found in the patent claims nor

Art Unit: 1633

are they obvious variants of such claims. Nothing in the patent claims leads one of ordinary skill in the art to the afore-mentioned limitations. The Examiner is apparently using hindsight by relying on teachings in the instant application. This too is improper.

Finally, MPEP 804(II) clearly states that double patenting is not to be confused with domination. Therefore to the extent that the Examiner may consider that the patent claims dominate, in whole or in part, the rejected application claims, this too is an improper basis for concluding that obviousness type double patenting exists.

For all of the foregoing reasons, a proper obviousness type double patenting rejection has not been made in view of the cited patent, and the rejected application claims are not obvious variants of the cited patent claims.

Applicant's arguments are acknowledged; however, the rejection is maintained for the following reasons:

Applicant argues that the claims must be found to be obvious over the patent claims independent of Craig. This is incorrect; an obviousness-type double patenting rejection can be made using a secondary reference (see MPEP 804 [R-5] II B).

Therefore, relying in Craig in making the instant rejection was proper.

Applicant argues that the passage indicated by the Examiner does not define terms in the cited patent claims. This is incorrect. The type of the immune response depends on the administration route. The indicated passage teaches mucosal delivery and mucosal delivery necessarily results in mucosal immune responses. Therefore, the passage does define the term "immune response" in the cited patent claims. Those

Art Unit: 1633

portions of the specification which provide support for the patent claims can be considered when addressing a double patenting rejection (see MPEP 804 [R-5] II B).

The Examiner's reliance on the above-cited passage is proper.

Applicant argues that, to the extent that the Examiner may consider that the patent claims dominate, this too is an improper basis for concluding that obviousness type double patenting exists. This argument is irrelevant to the instant rejection, which is not based on dominance.

For the reasons set forth above, the rejection is maintained.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142, and 144-146 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No. 6,239,116) in view of each Agrawal et al. (U.S. Patent No. 6,426,334), Briles et al. (U.S. Patent No. 6,042,838), Craig (U.S. Patent No. 6,689,757), Kincy-Cain et al. (Infection and Immunity, 1996, 64: 1437-1440) and Berzofsky et al. (U.S. Patent No. 6,749,856).

Krieg et al. teach a method of inducing a mucosal immune response in a subject by orally administering to the subject an oligonucleotide 8 to 100 nucleotides in length,

Art Unit: 1633

wherein the oligonucleotide can be administered by itself or concurrently with an antigen; the oligonucleotide has a sequence which includes the formula 5' $X_1X_2CGX_3X_4$ 3' wherein C is unmethylated, X_1 , X_2 , X_3 , and X_4 are nucleotides, the oligonucleotide contains phosphorothioate modifications at the 5' end or the 3' end, X_1X_2 could be GpT, and X_3X_4 could be TpT (claims 1, 4, 15-18, 136-139, and 141) (Abstract, column 6, lines 1-67, column 7, column 14, lines 3-32, column 28, lines 4-25, column 45, lines 36-42, column 46, lines 55-60). Krieg et al. teach that the administration of the oligonucleotide by itself results in an immune response; such an immune response would protect a subject from subsequent passive exposure to antigen (claim 138) (columns 6, lines 38-51). Krieg et al. teach that a non-oligonucleotide adjuvant could be included in the immunogenic composition (claim 8), that the antigen could be a protein, i.e., not encoded by a nucleic acid vector (claims 1, 20, 136, 137, 139, 141, 142, and 144-146) (column 7, lines 1-7, column 9, lines 48-53), and that the method could be used to induce an immune response in subjects to eliminate tumors or viral infections (claims 12, 13, 135, and 140) (column 10, lines 23-61). Krieg et al. teach administering the composition in conjunction with liposomes (claims 5-8) (column 13, lines 40-45, column 45, lines 6-17). Krieg et al. teach their oligonucleotide as having the formula 5' TCCATGTCGTTCCTGTCGTT3' (SEQ ID NO: 73), i.e., comprising the sequence 5' TCNTX₁X₂CGX₃X₄ 3' wherein N is 2 (claim 19) (column 32, Table 10). Krieg et al. also teach boosting with oligonucleotide to enhance the immune responses to the vaccines (claim 27) (column 47, lines 10-29). With respect to the limitation recited in claim 28, it

Art Unit: 1633

would have been obvious to one of skill in the art to include the non-nucleic acid adjuvant in the boost in order to improve the results.

Krieg et al. do not teach specifically the recited routes of administration recited in the instant claims 1, 136, 137, 139 and 141. However, at the time of filing such administration routes were taught by the prior art. For example Agrawal et al. teach inducing a mucosal immune response by administering oligonucleotides having a sequence including the claimed formula via intranasal or rectal administration (claims 1, 136, 137, 139, and 141) (column 5, lines 30-45, column 6, lines 48-50). It would have been obvious to one of skill in the art, at the time the invention was made, to substitute the oral administration of Krieg et al. with the intranasal or rectal administration of Agrawal et al. to achieve the predictable result of inducing mucosal immunity.

Although Krieg et al. and Agrawal et al. do not specifically teach that intranasal immunization results in mucosal immunity at remote sites (claim 26), this is an inherent feature of their method because the prior art teaches that intranasal administration results in mucosal immunity at remote sites. For example, Briles et al. teach that intranasal administration of antigens together with adjuvants results in induction and secretion of specific IgA antibodies in the digestive and genital tracts, i.e., remote mucosal immunity (column 8, lines 14-24, Examples).

Although Krieg et al. and Agrawal et al. teach the use of non-nucleic acid adjuvants, they do not specifically teach the adjuvants recited in claim 9. However, at the time the invention was made, such adjuvants were well known and used in the prior art. For example Briles et al. teach the use of saponins or cholera toxin and its B

Art Unit: 1633

subunit (column 4, lines 20-30, column 8, lines 14-18). It would have been obvious to one of skill in the art to use an adjuvant such as cholera toxin in the method of Krieg et al. and Agrawal et al. to achieve the predictable result of eliciting an immune response.

Krieg et al., Agrawal et al., and Briles et al. do not teach administering B-7 costimulatory molecule (claim 25). Craig teaches using B-7 to upregulate the immune response to vaccines (column 6, lines 35-49). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Krieg et al., Agrawal et al., and Briles et al. by further using B-7 costimulatory molecule, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to enhance the immune response elicited against the vaccine of interest. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that B-7 can be successfully used to potentate the immune responses to antigens.

With respect to the limitation recited in claim 129, it is noted that Krieg et al. teach their oligonucleotide as being capable of inducing IL-12 (column 6, lines 1-51, column 35, lines 50-67). The prior art teaches that IL-12 induces mucosal immune responses against intracellular pathogens and it is useful as a mucosal adjuvant for vaccines used to prevent or treat infectious with pathogens which gain entry via a mucosal surface (see Kincy-Cain et al., Abstract, p. 1437, column 1, second paragraph, p. 1439, column 2; Berzofsky et al., Abstract, column 3, lines 1-9, column 12, lines 36-50). Based on these teachings, one of skill in the art would have known that the

Art Unit: 1633

oligonucleotide of Krieg et al. is a mucosal adjuvant which could be used to treat subjects in need of mucosal immunization.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that the Examiner reliance on cites Belyakov et al. ignores the evidence of record that the role of IL-12 in mucosal immune responses was not clear at the time of filing.

As an example, Kincy-Cain et al. states that IL-12 can augment a mucosal immune response that arises after administration of intracellular pathogen *S. dublin*. However, the reference provides no data to evidence mucosal immune response induction, and instead infers mucosal immunity based on overall survival of the experimental subjects. The reference further speculates that IL-12 "most probably" exerts its effects through non-antigen-specific mechanisms including through IFN-gamma production by innate immune cells such as NK cells. Other references teach that IL-12 may not influence a mucosal immune response and/or that the role of IL-12 in this regard may vary depending on the route of administration. Some of these references indicate that mucosal immune responses occur even in the absence of IL-12. Simmons et al. (J. Immunol. 2002, 168:1804-1812) reports that IL-12 knockout (IL-12p40^{-/-}) mice mount gut-associated IgA responses after infection with *C. rodentium* (see for example Figure 6). The reference further reports that only a small fraction (10-15%) of the IL-12 knockout mice died post-infection, indicating that mice are able to

Art Unit: 1633

clear the infection independent of IL-12. The reference concludes that gut-associated IgA responses are not defective in IL-12 deficient mice. Arulanandam et al. (Vaccine 1999, 17:252-260), published after Belyakov et al., states that "(T)here is little information about the influence of IL-12 on mucosal immunity." (See page 252, second column, second paragraph). In support of this statement, the reference indicates that others have reported that intratracheal administration of IL-12 inhibits antigen-specific IgA in bronchoalveolar lavage (citing Yang et al. Nature Med. 1995 1:890-3) and that oral administration of IL-12 enhances serum IgG and has no effect on fecal IgA (citing Marinaro et al. J. Exp. Med. 1997 185:415-427). Arulanandam et al. themselves report no change in lung IgA levels and suppressed fecal IgA levels in mice immunized intranasally with DNP-OVA with cholera toxin B subunit and IL-12. The reference therefore shows that presence of IL-12 at a mucosal site does not induce mucosal IgA, and it further states that "only parenteral administration of IL-12 results in enhanced faecal IgA antibody levels." Marinaro et al. (J. Immunol. 1999, 162:114-121) documents that intranasal administration of IL-12 had no effect on mucosal secretory IgA responses to oral or nasal vaccines.

Applicant argues, that when the reference teachings are properly considered, the conclusion is that the role of (and thus the need for) IL-12 in mucosal immunity would not have been predictable to a person of ordinary skill in the art. Moreover, a person of ordinary skill in the art contemplating the use of IL-12 would not have known, been able to predict, or had a reasonable expectation of success relating to whether a mucosal administration route would be suitable. In fact, the cited art suggests that, at least in

Art Unit: 1633

some instances, a subject must be systemically exposed to IL-12 (e.g., via parenteral administration) rather than exposed at a mucosal surface.

As argued previously, Craig teaches away from the instant claims because Craig requires delivery of a nucleic acid that encodes an epitope (or antigen) while the rejected claims explicitly exclude such a limitation. The Examiner disregards this, and instead cites MPEP 2145 [R-6] XD for the proposition that "a teaching away from the invention is a teaching which renders prior art unsatisfactory for the intended purpose." Applicant assumes that the Examiner meant to cite MPEP 2145(X)(D) ("References Teach Away from the Invention or Render Prior Art Unsatisfactory for Intended Purpose" (emphasis added)) and will address the continued rejection on that assumption.

Applicant argues that the Examiner has narrowly defined a teaching away as "a teaching that renders prior art unsatisfactory for the intended purpose." This is incorrect. A teaching away is more broadly defined by the MPEP and the courts to be a teaching that "leads away" from a claimed invention. MPEP 2141.02(VI). (See also *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986) ("A reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered."); *Monarch Knitting Machinery Corp. V. Fukuhara Industrial & Trading Co., Ltd.*, 139 F.3d 977, 45 USPQ2d 1977 (Fed. Cir. 1998) ("A prior art reference may be considered to teach away when 'a person of ordinary skill, upon reading the reference, ... would be led in a direction divergent from the path that was taken by the applicant.'"). Thus, a teaching

Art Unit: 1633

away includes a teaching that leads one of ordinary skill away from the claimed invention. A teaching away does not only exist where a teaching renders prior art unsatisfactory for its intended purpose, as suggested by the Examiner.

The instantly rejected claims all require that the antigen not be encoded in a nucleic acid vector. A necessary feature of Craig however is administration of a nucleic acid that encodes an epitope. Thus Craig is clearly directing the person of ordinary skill in a direction opposite to that of the rejected claims, and it is therefore teaching away from the claimed invention. The teaching in Craig discourages a common limitation of the rejected claims, and it is therefore relevant to the issue of obviousness. In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

For at least these reasons, Applicant argues, the combination of references does not render obvious the rejected claims.

Applicant's arguments are acknowledged; however, the rejection is maintained for the following reasons:

Most of the Applicant's arguments are not new and were previously addressed. The new arguments are addressed below.

Applicant argues that, in relying on Belyakov et al., the Examiner ignores the evidence of record. This is incorrect. The evidence of record mentioned by Applicant was previously addressed. In making this argument, Applicant does not address the Examiner's reply in the non-final Office action mailed on 01/22/2009. Just because the evidence of record indicates that intranasally-administered IL-12 does not induce a

Art Unit: 1633

mucosal antibody response, does not mean that IL-12 cannot induce a mucosal immune response. First, the mucosal immune response comprises both an antibody and a CTL response; mucosally-administered IL-12 acts as an adjuvant to induce these CTLs (as evidenced by Belyakov et al. and Berzofsky et al.; see the non-final Office action mailed on 01/22/2009). Second, the evidence of record relied on by the Applicant demonstrates that it is only the administration at the mucosal site which does not induce mucosal IgA; parenteral administration of IL-12 is capable of inducing results in enhanced IgA. Krieg et al. teach that administering their oligonucleotide to a subject orally (i.e., mucosal) induces IL-12 into the subject (i.e., parenteral) (column 6, lines 1-51, column 35, lines 50-67, column 45, lines 55-61). The instant rejection is not based on mucosal administration of IL-12. Rather, the instant rejection is based on mucosal administration of the oligonucleotide as taught by Krieg et al., which would induce parenteral IL-12. Based on the prior art as a whole, one of skill in the art would have known that parenteral administration of IL-12, as taught by the combination of prior art cited above would result in mucosal immunity. For these reasons, Applicant's argument of lack of predictability and reasonable expectation of success is not found persuasive.

Applicant argues that the Examiner has narrowly defined a teaching away. While this might be true, this does not change the Examiner's statement made in the non-final Office action mailed on 01/22/2009 that, to teach away from the claimed invention, the art must indicate that using protein vaccines in conjunction with B-7 would not result in an immune response. In fact, there is no teaching or suggestion in the art that B-7 would not be effective with antigens which are not encoded by nucleic acids. Just

Art Unit: 1633

because Craig's invention relates to DNA vaccine, does not mean that B-7 cannot be used in the method of Krieg et al.; there is no such teaching in Craig. Apart from an argument, Applicant did not provide any evidence to this effect. For these reasons, Applicant's argument of teaching away is not found persuasive.

In conclusion, the claimed invention is rendered *prima facie* obvious by the combination of art cited above and the rejection is maintained.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

Art Unit: 1633

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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